Is Progression of Pulmonary Fibrosis due to Ventilation-induced Lung Injury?

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Pulmonary fibrosis can develop in association with genetic variants, occupational and environmental exposures, adverse reactions to numerous medications, and many connective tissue diseases, and it can also be idiopathic. Subclassifications of pulmonary fibrosis are identified on the basis of clinical presentations, roentgenographic manifestations, and/or histology. Wnt (Wingless/integrase 1) activation of c-Jun and β-catenin has been suggested as a unifying molecular pathway resulting in fibrosis because c-Jun and β-catenin upregulate expression of many profibrotic factors (1), but little is known about what activates these pathways or the mechanism(s) explaining what appears to be a self-sustaining temporal and spatial progression of injury.

Ventilator-induced lung injury (VILI) contributes to the mortality of the acute respiratory distress syndrome by two putative mechanisms that are not mutually exclusive. The first is the mechanical stress on epithelial cells that occurs as a result of cyclical opening and closing of collapsed alveoli and/or small airways during the ventilatory cycle (termed "atelectrauma"). The second is the mechanical strain on epithelial cells in alveoli that are adjacent to areas of airspace collapse when these alveoli approach their maximum volume owing to parenchymal interdependence (termed "volutrauma"). This strain can also occur in the absence of collapse as a result of high transpulmonary pressures. Because airspace collapse can occur during spontaneous breathing as well as during mechanical ventilation, we are defining VILI as ventilation- rather than ventilator-induced lung injury.

The purpose of this perspective article is to summarize information supporting the hypothesis that VILI can be a unifying pathogenic process explaining the self-perpetuating injury and progression of pulmonary fibrosis (Figure 1). We review studies demonstrating that alveolar collapse has been a repeatedly observed pathologic finding in pulmonary fibrosis, thereby providing a setting in which VILI can occur. We summarize studies showing that in patients with pulmonary fibrosis, many of the risk factors and genetic variants related to the condition, as well as most of the models used to study it, are associated with surfactant abnormalities and/or with AT2 (alveolar type 2) cell injury that could result in surfactant abnormalities, thereby providing an explanation for why collapse develops. We also estimate the mechanical strain resulting from volutrauma and speculate about some potential clinical implications suggested by this proposed pathophysiology.

Atelectasis in Pulmonary Fibrosis

If VILI contributes to pulmonary fibrosis, then cyclical and/or permanent alveolar collapse must be part of the pathology. Burkhardt and Cottier (2) date the first discussion of alveolar collapse in pulmonary fibrosis to a German textbook of pathology published in 1922 in which Kaufmann (3), under the heading "Collapse Induration," noted that "if collapse of alveoli persists for some time, expansion may no longer be possible. The denuded alveolar walls stick together and coalesce. The alveoli are obliterated. In the interstitial tissue proliferation of fibrous tissue ensues resulting in cicatricial induration." Burkhardt (4) and Burkhardt and Cottier (2) also cited multiple papers in the German literature dating to the 1950s that described collapse induration as an important mechanism in the development of pulmonary fibrosis.

Heppleston's 1956 publication (5) seems to have been the first to suggest that

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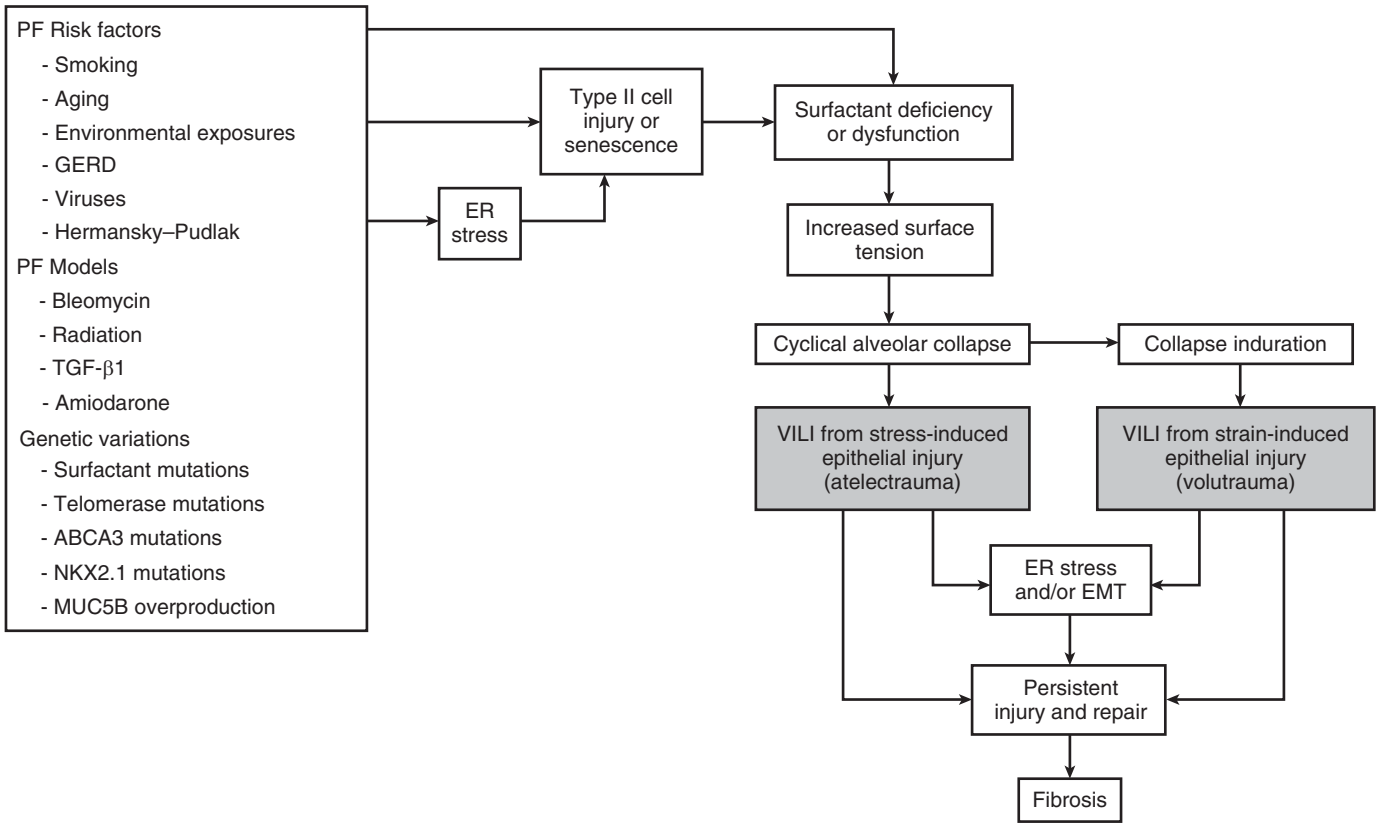

Figure 1. Proposed pathogenesis of pulmonary fibrosis (PF) progression resulting from ventilation-induced lung injury (VILI). Surfactant abnormalities can occur directly (e.g., surfactant gene variant and smoking) or indirectly as a result of alveolar type II cell injury, which, in turn, can also occur directly (e.g., radiation) and/or through endoplasmic reticulum (ER) stress (e.g., SP-A or SP-C mutations). Mechanotransduction can cause progression of fibrosis by several mechanisms, including directly damaging cell membranes, changing the cytoskeletal structure, and/or activating ion channels. Each of these effects activates different signaling pathways, resulting in production and release of cytokines and chemokines, ER stress, and/or epithelial–mesenchymal transition (EMT). GERD = gastroesophageal reflux disease; TGF-β = transforming growth factor-β.

the airspace dilation seen with honeycombing results from alveolar collapse that produces locally exaggerated traction during inhalation in adjacent lung. Spencer (6) and subsequently numerous other investigators (2, 4, 7–10) proposed that the damage to alveolar lining cells that occurs in pulmonary fibrosis reduces surfactant, thereby increasing the tendency for alveoli to collapse.

Katzenstein (7), studying acute interstitial pneumonitis with electron microscopy, found many partially collapsed alveoli, others that were completely collapsed with permanent apposition of their septa, and still others that were abnormally large and dilated. She suggested that these changes were early events in the pathophysiology of the fibrosis and that the collapse could cause or contribute to the decrease in lung volume that occurs. In support of the findings of Heppleston (5) noted above, Katzenstein also suggested that the dilated alveoli could explain the honeycombing appearance in end-stage disease and that it resulted from a "traction-like phenomenon" around the permanently collapsed alveoli. Snider and colleagues (11) similarly attributed the airspace enlargement seen in cadmium chloride–induced lung fibrosis to atelectatic lung regions generating forces on adjacent uninvolved alveoli. Basset and colleagues (12) subsequently reported the same ultrastructural findings noted by Katzenstein (7) in hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF), the fibrosis occurring in conjunction with connective tissue diseases, chronic eosinophilic pneumonia, drug and radiation pneumonitis, and chronic organizing pneumonia, and Myers and Katzenstein (13) observed the same alveolar collapse in a patient with usual interstitial pneumonia (UIP).

Crouch (14) described the pathophysiology of pulmonary fibrosis as involving "alveolar collapse, in which airspaces are transiently or permanently obliterated secondary to apposition of the alveolar walls" and, together with Burman and colleagues (15), concluded that honeycombing and the bronchiectasis seen in the disease resulted from the alveolar collapse with traction on the adjacent lung tissue. Galvin and colleagues (8) suggested that injury to the alveolar epithelium altered surfactant and increased surface tension, leading to collapse of smaller alveoli into larger alveolar ducts, with the collapsed alveolar walls becoming permanently opposed in a self-perpetuating fashion. They implicated alveolar collapse as the main contributor to the progression of fibrosis and also attributed the preferential distribution of honeycombing in the posterior basal lung segments to alveoli in these regions being smaller at end

exhalation and accordingly being the ones most likely to collapse. The preferentially basal distribution of honeycombing could also be the result of the increased transpulmonary pressure swings that occur in this region during ventilation (16–18).

Leslie (19) defined recurrent tractional injury as alveolar collapse and rapid reopening during respiration of the basal lobules. Although not referring to VILI *per se*, she suggested that tractional injury occurring over many years in response to inherited or acquired surfactant abnormalities could represent a unifying hypothesis explaining the pathogenesis of pulmonary fibrosis. The timing of changes in surfactant and stereology after bleomycin-induced pulmonary fibrosis led Lutz and colleagues (20) to conclude that surfactant abnormalities were the *cause* of the alveolar collapse and collapse induration rather than the *effect* of the fibrosis.

Todd and colleagues (21) reviewed a previously recognized discrepancy between what appears to be extensive collagen deposition based on microscopic examination of lungs with fibrosis and the results of a number of studies that showed either no increase or only a minor increase in total collagen/unit of dry weight. They suggested that alveolar collapse accounted for this discrepancy because the opposed alveolar walls would appear as fibrosis microscopically. They agreed with earlier investigators that the alveolar collapse was responsible for overdistention of uninvolved alveoli or airspaces adjacent to the collapse and that this process accounted for the anatomic heterogeneity of the fibrotic process. Todd and colleagues (21) concluded that collapse induration was a better explanation for the pathophysiological findings than dysregulated fibroblast proliferation leading to excess matrix accumulation and that therapies aimed at preventing collapse would more likely be beneficial than treatments focused on inhibiting fibroblast replication and matrix accumulation.

Burkhardt (4, 22) proposed a comprehensive pathophysiological schema for the development of pulmonary fibrosis that involved epithelial injury leading to surfactant deficiency, alveolar collapse, collapse induration, and overexpansion of adjacent lung parenchyma, resulting in fibrosis. We have modified Burkhardt's schematic to emphasize that *1*) surfactant abnormalities and/or injury to AT2 cells that would predispose to surfactant abnormalities have been described in patients with pulmonary fibrosis, as well as with many of the risk factors, models, and genetic variations associated with pulmonary fibrosis, and *2*) that the atelectasis and collapse induration resulting from the surfactant abnormality predispose patients to VILI from stress (atelectrauma) and/or strain (volutrauma) (Figure 1).

Type I cells are preferentially stretched with lung inflation as type II cells are partially protected by surfactant accumulation in alveolar corners (although a number of studies have examined the effect of strain on inflammatory mediator release using isolated type II cells). Stretching epithelial cells by 5–17% without causing damage can increase cellular proliferation as well as production of surfactant, prostacyclins, and numerous other proinflammatory and profibrotic cytokines. Multiple mechanisms by which these effects occur have been described. Lung strain activates mechanosensitive ion channels, resulting in calcium influx and activation of tyrosine kinases. Strain can also cause calcium influx directly by disrupting cell membranes, thereby activating transcription factors (e.g., c-Fos), leading to translocation of NF-κB (nuclear factor-κB) to the cell nucleus. Strain activates integrins in the cytoskeleton, which, in turn, control NF-κB activity via effects on mitogen-activated protein kinases, other transcription factors, and NF-κB kinase (23). These signaling pathways can lead to release of inflammatory and profibrotic cytokines (e.g., TGF-β1 [transforming growth factor-β1], TNF-α [tumor necrosis factor-α], IL-6, IL-8, and IL-10), prostanoids (e.g., PGI_2 [prostaglandin I_2], $PGF_{2\alpha}$, PGD_2, PGE_2, and thromboxane B_2) via induction of phospholipase A_2, and chemokines (e.g., macrophage inflammatory protein and macrophage chemotactic protein 1), thereby causing ongoing fibrosis (24–31). Integrin signaling is also linked with epithelial–mesenchymal transition, c-Jun signaling, and the Wnt/β-catenin pathway (32–36). In a genome-wide study of patients with pulmonary fibrosis, Fingerlin and colleagues (37) identified variants of two genes (DSP [desmoplakin] and DPP9 [dipeptidyl peptidase 9]) that counter the effects of mechanical stress on cell adhesion, and the DSP variant also alters the Wnt/β-catenin pathway. Integrin signaling is also associated with endoplasmic reticulum (ER) stress, and markers for ER stress have been found in response to mutations affecting SP-A (surfactant protein-A), SP-C, and the ABCA3 (ATP-binding cassette transporter A3) gene; in many of the conditions associated with pulmonary fibrosis, including aging, viral infections, cigarette smoke (CS) exposure, and inhalational injuries; and in some animal models of the disease (37–42). ER stress can also occur in response to mechanical stress alone, as would occur with VILI (15, 34, 42).

Surfactant and/or AT2 Cell Abnormalities in Patients with Pulmonary Fibrosis

Patients with Pulmonary Fibrosis

In the BAL fluid (BALF) obtained from patients with pulmonary fibrosis, surfactant phospholipids are decreased; the phospholipid profile is altered; and SP-A concentrations are markedly reduced (43–48). Günther and colleagues (47) and Schmidt and colleagues (48) also found that the surfactant obtained from patients with IPF had markedly impaired adsorption ability and reduced surface tension–lowering activity.

Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome (HPS) results from abnormal formation or trafficking of lysosome-related organelles. The phenotype for HPS types 1 and 4 includes pulmonary fibrosis, and a milder form of fibrosis occurs in type 2. Humans with HPS and murine models of HPS have impaired secretion of lamellar bodies (LBs), resulting in giant LBs appearing in AT2 cells; ER stress; and decreases in surfactant phospholipids and SP-B and SP-C, the two proteins most closely linked to the surface tension–lowering activity of surfactant (Table 1) (49–51). Guttentag and colleagues (50) found that the surface tension–lowering activity of surfactant was not impaired in BALF obtained in a mouse model of HPS at 10–15 weeks of age. Mahavadi and colleagues (51), however, noted a marked reduction in surface activity in BALF obtained at both 3 and 9 months, together with increases in SP-B and SP-C in lung tissue and marked progression of fibrosis between 3 and 9 months. They proposed that fibrosis developed because of reduction in surfactant and the resulting increase in surface tension and attributed the difference in their results from those of Guttentag and colleagues (50) to studying the mice over a longer period of time. This explanation may have relevance to the observation that pulmonary fibrosis,

Table 1. Surfactant and Surfactant-Regulator Functions

Surfactant	Functions
SP-A	Primarily functions as a collectin Involved in formation of tubular myelin Contributes to adsorption of phospholipids at air–liquid interface Contributes to regulating phospholipid synthesis, secretion, and recycling in alveolar macrophages Counteracts the inhibitory effects of proteins on the surface tension–lowering function (recent data question the effect of proteins on surface tension, however [165])
SP-B	Stabilizes the phospholipid monolayer Reduces surface tension by facilitating insertion of phospholipids into the alveolar lining layer Assists in formation of tubular myelin Interferes with the intermolecular forces of water Organizes lamellar body structure Promotes lamellar body exocytosis from AT2 cells
SP-C	Increases adsorption of phospholipids to the air–liquid interface Inserts into the monolayer and squeezes out only at high surface tension Involved in organization and packaging of phospholipid membranes in lamellar bodies Stimulates surfactant recycling by AT2 cells
ABCA3	Regulates lamellar body formation by moving cholesterol and phospholipids across lamellar body membranes Involved with SP-B and SP-C processing
Thyroid transcription factor 1 (also known as NKX2-1)	Controls expression of genes coding for SP-A, SP-B, SP-C, and ABCA3

Definition of abbreviations: ABCA3 = ATP-binding cassette transporter A3; AT2 = alveolar type II; SP = surfactant protein.

particularly IPF, occurs much more commonly in older patients (52) (*see below*).

Surfactant and/or AT2 Cell Abnormalities Associated with Risk Factors for Pulmonary Fibrosis

Smoking

Cigarette smoking is a strong risk factor for pulmonary fibrosis (53). Miller and Bondurant (54) assessed surface tension properties of rat lung extracts and BALF before and after exposure to CS and found that CS decreased the ability of surfactant to stabilize alveoli. Cook and Webb (55, 56) found that CS reduced hysteresis and increased surface tension at low surface areas. Surfactant phospholipids are decreased in the BALF of smokers compared with nonsmokers (57–63), and Finley and colleagues (58) found that phospholipid concentrations returned to normal in as little as 2 weeks after smoking cessation. Chronically exposing rats to CS selectively decreases SP-B concentrations (63). After exposing rats to 25 days of inhaled CS, Le Mesurier and colleagues (59) found areas of expanded alveoli that were contiguous with areas of alveolar collapse associated with increased interstitial connective tissue and increased numbers of LBs in AT2 cells.

Aqueous extracts of CS cause senescence of AT2-like A549 cells and in AT1 and AT2 cells *in vitro* and *in vivo* (64). CS also causes apoptosis of A549 cells (65) and inhibits stimulated surfactant secretion from AT2 cells (66). Smokers also have increased expression of MUC5B (mucin 5B) (67) and shortened telomeres (68, 69) (*see below*).

Environmental Exposures

A number of epidemiological studies document an association of metal or wood dust pollution and other occupational exposures with pulmonary fibrosis, and mineral dust, components of pollution, and other ultrafine particles alter the adsorption and the surface tension–lowering activity of surfactant (70–77). Organic dust exposure reduces SP-A, SP-B, and SP-C expression in epithelial cells by inhibiting thyroid transcription factor 1 (*see below*) (78).

Microbial Agents

Epstein-Barr virus, cytomegalovirus, and herpesviruses have been associated with pulmonary fibrosis. The effects of these viruses on surfactant have not been investigated, but Epstein-Barr virus is known to infect, replicate in, and cause apoptosis of AT2 cells and to reduce AT2 cell proliferation (39, 79–80), which could affect surfactant production and/or recycling.

Gastroesophageal Reflux Disease

Whether gastroesophageal reflux disease is a risk factor for pulmonary fibrosis is debated, but patients with gastroesophageal reflux disease have reduced SP-A and SP-D in their BALF as well as alterations in their surfactant phospholipid profile (81, 82).

Aging

Age is a key risk factor for developing IPF because the majority of patients are not diagnosed until their sixth decade (52). Although there are no studies establishing a direct link between aging and surfactant abnormalities, considerable data link telomere length and AT2 cell senescence to PF (*see below*).

Surfactant and/or AT2 Cell Abnormalities Associated with Genetic Variants Causing Pulmonary Fibrosis

SP-A

Patients with SP-A mutations are reported to be predisposed to developing pulmonary

fibrosis (83–85). SP-A mutations generate ER stress, and surfactant obtained from SP-$A^{-/-}$ mice has increased minimum surface tension at low phospholipid concentrations (85, 86).

SP-B

The pathological findings in lungs of patients with SP-B mutations include alveolar proteinosis, desquamative interstitial pneumonia (DIP), enlarged AT2 cells, and fibroblast proliferation. Patients and mice with SP-B variants have abnormal-appearing LBs, complete absence or reduced amounts of SP-B in the BALF and lung tissue, an altered phospholipid profile, and interruption in processing the precursor to SP-C, and their BALF has a reduced ability to decrease surface tension (87–92).

SP-C

Mutations in the SP-C gene have been reported to be associated with diffuse alveolar damage, nonspecific interstitial pneumonia (NSIP), DIP, UIP, AT2 cell hyperplasia, and honeycombing (87). SP-C mutations can cause misfolding and accumulation of the SP-C precursor that results in ER stress (93–96), reduced or no SP-C in the alveolar space, abnormal hysteresis, and abnormal surface tension lowering (97–99). Experimentally regulated expression of an SP-C mutation results in acute alveolar inflammation followed by fibrosis without evidence of AT2 cell apoptosis, suggesting that abnormalities in surfactant may also cause fibrosis in the absence of ER stress (95).

ABCA3

Patients with ABCA3 mutations present with alveolar proteinosis, DIP, UIP, or NSIP. Phospholipid profiles are abnormal with decreased phosphatidylcholine as well as decreased or absent mature SP-B and SP-C in the pulmonary interstitium and BALF, and minimum surface tension is increased (100–107).

Thyroid Transcription Factor 1 (NKX2-1)

Patients with mutations in NKX2-1 (thyroid transcription factor 1) develop respiratory failure, alveolar proteinosis, and fibrosis as part of the brain-thyroid-lung syndrome. Promoter activity for SP-A, SP-B, SP-C, and ABCA3 in AT2 cells is altered by NKX2-1 mutations (108–114).

Telomeres

Chromosomes normally shorten with each cell division, ultimately activating a DNA damage response that leads to cell senescence or death. Telomeres are located on the ends of the chromosomes and limit the rate of shortening. Telomerase helps maintain telomeres, and mutations in telomerase genes result in more rapid telomere shortening. Telomerase mutations are found in 8–30% of patients with a family history of IPF, in 1–25% of patients with sporadic IPF, and in 12% of patients with the pulmonary fibrosis associated with rheumatoid arthritis (115–119). They have also been associated with NSIP, acute interstitial pneumonitis, and other subtypes of pulmonary fibrosis (119). Approximately 20% of patients with dyskeratosis congenita (a disease caused by telomerase mutations) develop pulmonary fibrosis (120). Telomerase activity falls 72 hours after bleomycin administration, linking short telomeres to the fibrosis that develops in this model (121). Waisberg and colleagues (9) suggested that abnormal telomerase expression reduces the number of AT2 cells, which, in turn, reduces surfactant production, leading to alveolar collapse and fibrosis. Alder and colleagues (122) demonstrated that telomere dysfunction induced AT2 cell senescence.

MUC5B

MUC5AC and MUC5B are the major mucins in airway secretions. MUC5B is produced by submucosal glands and goblet cells in the tracheal and bronchiolar epithelia as well as by AT2 cells, and its production is enhanced in patients with pulmonary fibrosis. MUC5B overproduction as a result of a common variant (rs35705950) in the promoter of the gene accounts for approximately 30% of patients who develop IPF and is also associated with the interstitial fibrosis seen in rheumatoid arthritis (123, 124). Injection of gastric mucins or recombinant MUC5B into alveoli raises surface tension (125), as was previously theorized by van Moorsel and colleagues (126). Additional research is needed to understand whether the gain-of-function promotor variant that increases expression of MUC5B in bronchioles alters surfactant properties in the alveolus.

Surfactant and/or AT2 Cell Abnormalities in Models of Pulmonary Fibrosis

Bleomycin

Several groups have documented changes in surfactant-associated phospholipids and proteins that correlate with the changes in physiology occurring after bleomycin (127–132). Marked downregulation of SP-B and SP-C occurs as early as 2 days after bleomycin administration, persists during the fibrotic period, and correlates with the reduction in the surface-active properties of surfactant (128, 129). The inflammatory response and/or the volutrauma that occurs after bleomycin involves upregulation of TGF-β1 and TNF-α, both of which downregulate SP-B and SP-C expression and increase surface tension (132–134). Surfactant abnormalities seem to be a required element for bleomycin-induced fibrosis because stimulating AT2 cell proliferation with keratinocyte growth factor or restoring SP-C expression with a histone deacetylase inhibitor protects against the fibrosis (135–139).

Radiation

LBs in AT2 cells are markedly depleted 1–24 hours after a single dose of radiation. At 7 days, AT2 cell hypertrophy occurs with increases in the number of LBs and signs of AT2 cell degeneration (i.e., vacuolation, mitochondrial swelling, and distention of the ER). Sloughing of the cells into the alveoli occurs up to 1 month later together with reduced surfactant turnover (140–143). The early loss and subsequent increase in LBs correlates with the amount of surfactant phospholipids in the BALF and with the synthesis and metabolism of the phospholipids (141, 144). In humans, phosphatidylcholine concentrations decline, but the two-phase response may not occur (145, 146). BALF obtained from humans approximately 1–4 months after irradiation has altered concentrations of various surfactant phospholipid components and markedly reduced the ability to lower surface tension (144, 145, 147). At 6–12 months, atelectasis develops (144).

TGF-β1

Adenoviral transfer of TGF-β1 via the airway results in gene expression that peaks at 7 days, at which time decreased

compliance is observed together with increased surface tension, reduced SP-B and SP-C expression, marked alveolar collapse, and increased alveolar size heterogeneity without an increase in collagen. These changes are followed by progressive fibrosis that continues through at least 9 weeks (135, 148, 149). Intratracheal administration of surfactant at 3 and 6 days reduces these changes.

Amiodarone

Amiodarone causes pulmonary fibrosis, interstitial inflammation, and AT2 cell hyperplasia. SP-B and SP-C accumulate in the AT2 cells and alveoli, and ER stress and autophagy-dependent AT2 cell apoptosis occur (150, 151,). Amiodarone also results in collapse induration in association with surfactant dysfunction that is manifested by an increase in minimum surface tension (152).

Alveolar Micromechanics in Pulmonary Fibrosis

Cyclical airspace opening and closing with ventilation can occur in airways and/or alveoli. Because epithelial damage in the airways is not generally seen in pulmonary fibrosis, atelectrauma affecting the airways would seem to be unlikely. Atelectrauma affecting alveoli, however, has been implied by many investigators. Katzenstein (7) indicated that partial alveolar collapse was more prominent than collapse of the entire alveolus. Burkhardt's schematic (4, 22) indicated that reversible alveolar collapse occurred before the time it became permanent. Crouch (14) noted that alveolar collapse could be transient or permanent, and Leslie (19) indicated that collapsed alveoli were pulled open during inhalation. In a single study in bleomycin-treated rats, however, only minimal alveolar recruitment and derecruitment occurred because the transpulmonary pressures generated did not reach the threshold necessary to reopen collapsed alveoli during tidal breathing (20). We have elected to model the strain resulting from permanent alveolar collapse (i.e., volutrauma) rather than the stress from atelectrauma, because the latter would vary with ventilation, would potentially be related to the flow and duration of inhalation, and would be inversely related to the opening pressure of any given alveolus. In addition, Yen and colleagues (18) noted that the major micromechanical alteration occurring in a ventilator-induced model of lung injury was strain affecting the epithelial cells in alveoli adjacent to those that were permanently collapsed.

Collapse of one alveolus will distend the neighboring alveoli via tractional forces resulting from parenchymal interdependence. Mead and colleagues (153) calculated that a fully collapsed alveolus could increase distending pressure in adjacent patent alveoli fivefold. This phenomenon is well documented at the alveolar/septal scale in isolated lungs in response to alveolar flooding (154), at greater scale in fixed tissue as described above, and in the increased V_A and V_A variability measured in animal models of pulmonary fibrosis (10, 155–157).

Finite element simulations employing an idealized network of alveoli (155) show that the stiffening of a single central alveolus, or a cluster of alveoli, without reducing V_A intensifies septal wall strain in the remaining patent alveoli. Because the morphology of pulmonary fibrosis is characterized by alveolar collapse, where V_A approaches zero, we have included finite element simulations of an idealized alveolar network that is based on a previously published model (157) and described in the online supplement (Figure E2). The model shows that a single collapsed and stiffened alveolus, representing an atelectatic alveolus, raises the maximum septal strain (ε_{max}) at FRC to nearly equal the septal strain predicted at TLC in the open portions of the normal lung.

Expanding the number of atelectatic alveoli results in further increases in ε_{max}. Figures 2C–2E show that the strain increase occurs in a localized area covering only a few alveoli, and this region grows with the size of the atelectatic region, indicating that both the magnitude and area of increased strain expand during the progression of fibrosis.

It is important to note that the alveoli adjacent to the collapsed alveolus in Figure 2C have an average area that is 13% less than that of the open alveoli farther from the collapsed alveolus. Likewise, although the alveoli adjacent to the collapsed region in Figures 2D and 2E have areas 15% and 33% smaller, respectively, than those of the far-field alveoli, it is the strain on the alveolar septa, not the V_A, that causes overdistention-induced damage. Because the tethering-induced strains in these adjacent septa at FRC are greater than septal strains predicted at TLC in the open lung, it is likely that the basement membrane is distended and that the increased length is not due solely to the unfolding of septal pleats (158). *In vitro* studies indicate that this degree of strain will cause inflammation (159), increased permeability (160), epithelial–mesenchymal transition (32), and cell death (161).

In simulated networks in which a contiguous pathway of strained septa is present, force transmission can occur over longer distances (157), which is an important consideration because the fibroblast foci seen in pulmonary fibrosis may form an interconnected network (162) that may facilitate long-range force coupling. Although there are conflicting data on this point (163), if the fibroblastic foci do not form an interconnected network, then transmission of force through the stiffened foci will still extend through large regions of the parenchyma.

Speculations

To our knowledge, there are no data describing the extent of lung strain needed to cause pulmonary fibrosis. Alveoli can increase in size without increasing strain because of septal unfolding up to perhaps 80% of TLC. Above that point, however, further expansion stretches the basement membrane and increases strain. Because epithelial injury is known to increase with the frequency and amplitude of the stretch, we would reason that the relationship between strain and fibrosis could be represented as follows: pulmonary fibrosis $\approx$ strain $\cdot f \cdot t$, with strain having to be above the threshold that initiates mechanotransduction and f and t representing the frequency and duration, respectively, over which the strain is applied. Because it takes years, if not decades, for fibrosis to develop, we would also reason that only a minimal increase in strain would be sufficient to cause fibrosis because it would be applied for so long. Our model (Figure 2) suggests that, in the setting of a single atelectatic alveolus, the septal strain in adjacent alveoli increases 30% when the lung is at its normal resting volume. When seven alveoli are atelectatic, septal strain in adjacent alveoli increases 50% at resting volume. This implies that strain would be increased at normal

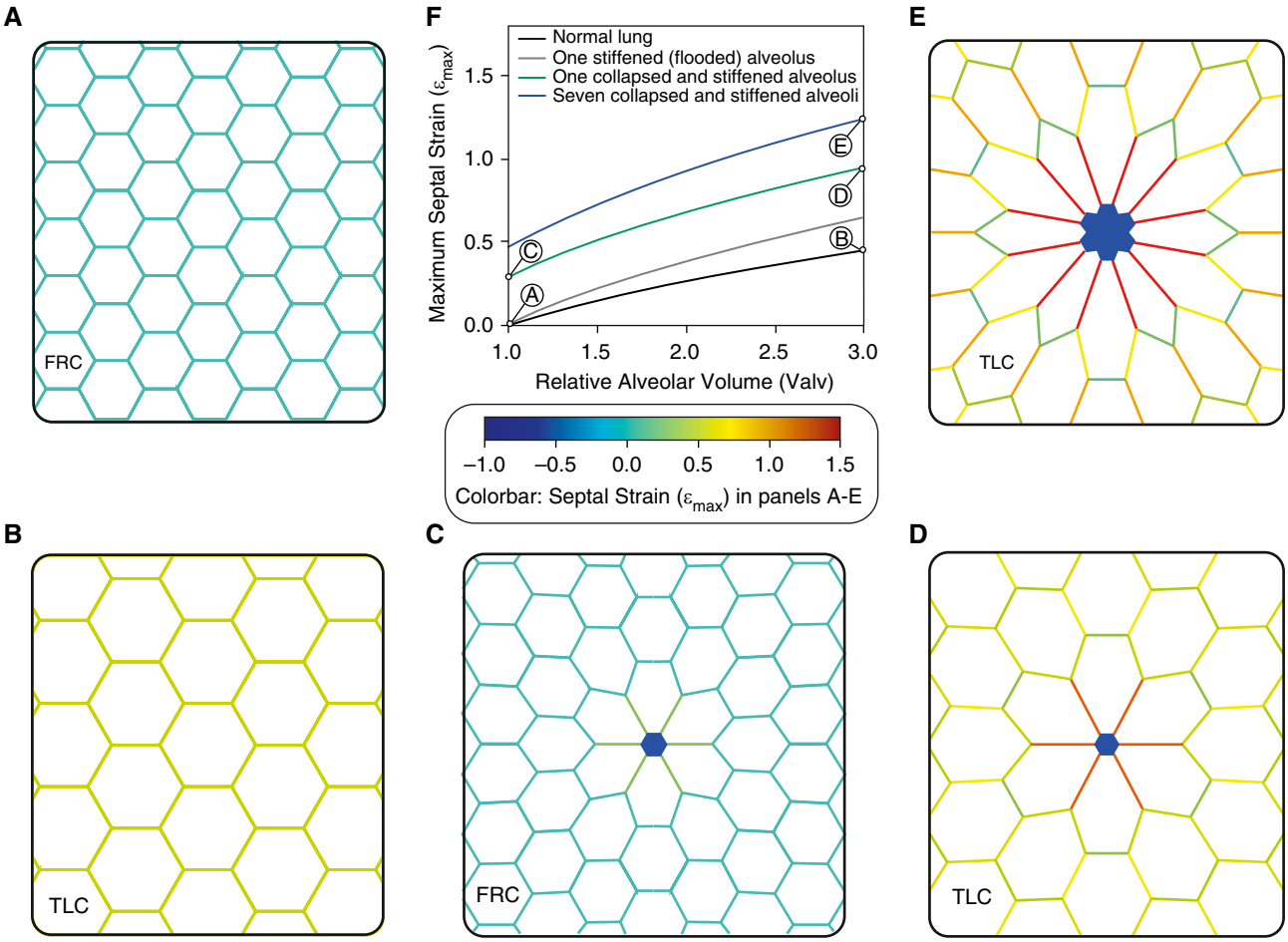

Figure 2. Maximum alveolar septal strain (ε_{max}) increases with alveolar collapse. (*A*) The undeformed finite element domain represents the linear elastic alveolar network at FRC. (*B*) Tripling the lung volume above the resting state, which we equate to a deep inspiration (e.g., TLC), corresponds to a cross-sectional area that is $3^{2/3}$ times that at FRC, assuming that the expansion of the lung is isotropic. (*F*) Stiffening a single alveolus by a factor of 100 to simulate flooding (gray) does not affect strain at FRC and causes a moderate increase at TLC. (*C* and *F*) A collapsed and stiffened (i.e., atelectatic) alveolus is represented by reducing the resting area by 90% and increasing the elastic modulus 100-fold (*C*) to yield an ε_{max} at FRC that is approximately equal to ε_{max} at TLC in the open network (*F*). (*D*) Inflating the network to TLC with a single atelectatic alveolus yields a 2.5-fold increase in ε_{max} compared with the open network. (*E* and *F*) Increasing the number of atelectatic alveoli (*E*) increases ε_{max} at both FRC and TLC compared with a single collapsed alveolus (*F*). The color bar indicates strain in the alveolar septa shown in *A*–*E*.

transpulmonary pressures in the setting of collapse induration.

The pathophysiology we propose suggests that, other than preventing or reducing the initial AT2 cell injury, restoring surface tension with exogenous surfactant might be a beneficial intervention, as was first suggested by Katzenstein (7) and subsequently by others (47, 138). Exogenous surfactant would not be able to reverse permanent alveolar collapse and, accordingly, would have little to no effect on volutrauma-related strain caused by existing collapse induration and would not be able to restore denuded epithelium in these alveoli. Surfactant administration could, however, slow progression of the fibrosis by reducing atelectrauma-related strain and, in turn, interdependence-induced volutrauma in adjacent alveoli (Figure 2). In addition, and perhaps more important, recent advances in defining genetic risk factors for pulmonary fibrosis would allow surfactant to be administered in prophylactic fashion to at-risk patients before development of extensive alveolar collapse or fibrosis (164). Finding a practical and safe way to accomplish what would seemingly have to be lifelong administration in spontaneously breathing patients would be challenging, but nebulized surfactant has recently shown some acute benefits in laboratory studies and neonates.

The pathophysiology described also leads to the question whether patients with pulmonary fibrosis should be instructed to avoid large inhalations or large transpulmonary pressure swings as would occur during vigorous exercise. Doing so could reduce the stress associated with atelectrauma and the strain associated with volutrauma, akin to the recommendation that patients with acute respiratory distress syndrome be treated with low V_T, because we suggest that the pathogenesis of VILI in the two conditions is the same (17, 18). Stretching the epithelium is the strongest stimulus to surfactant secretion by AT2 cells, however, such that large breaths could also reduce atelectrauma and prevent newly

collapsed alveoli from becoming permanently collapsed. The net effect of large tidal excursions could perhaps depend on the relative contribution of the mechanical stress versus strain in any given individual. Another factor to consider with regard to advising patients is that pulmonary fibrosis progresses over years, if not decades, and patients spend only a limited amount of time each day or week doing vigorous exercise. Finally, the physiological and psychological benefits of regular exercise, together with the fact that the pathophysiology described is currently an untested hypothesis that lacks even a single study demonstrating proof of concept, lead us to conclude that making any recommendation regarding limiting the frequency or intensity of exercise is premature.

Conclusions

The existing paradigm explaining the pathophysiology of pulmonary fibrosis involves AT2 cell injury as an early event with subsequent recurrent injury (and repair) leading to progressive fibrosis. We suggest that surfactant abnormalities occur as a direct effect of various risk factors and/or genetic variations associated with pulmonary fibrosis, or indirectly as a result of AT2 cell injury. These surfactant abnormalities and potentially other environmental, genetic, and pathogenic features of pulmonary fibrosis cause alveolar collapse, and the resulting stress and strain of ongoing ventilation (i.e., VILI) can provide a unifying explanation for the progressive injury that occurs. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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